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(57) Abstract: A pharmaceutical composition, comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier in the pharmaceutical composition and the use of such a composition in medicine.

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NOVEL COMPOSITION AND USE

This invention relates to novel compositions, in particular to compositions containing more than one active ingredient and their use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Biguanide antihyperglycaemic agents are commonly used in the treatment of non-insulin dependent diabetes mellitus (NIDDM, or Type 2 diabetes). 1,1-Dimethylbiguanidine (or metformin) is an example of a biguanide antihyperglycaemic agent.

European Patent Application Publication Number 0 306 228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0 306 228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter referred to as "Compound (I)"). European Patent 0 658 161 discloses certain salts of Compound (I) including the maleate salt at Example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as "insulin sensitisers". In particular Compound (I) is a thiazolidinedione insulin sensitiser.

The above mentioned publications are incorporated herein by reference.

An important consideration in the preparation of formulations containing a combination of active agents is the stability of the active agents given that mutual interaction of the agents themselves or the agents with excipients can lead to instability of the agents.

Metformin is most commonly administered in the form of its hydrochloride salt (or metformin HCl). It is indicated that in certain formulations Compound (I) is prone to decomposition, both during preparation and storage, due to the presence of metformin hydrochloride. We now provide pharmaceutical compositions containing Compound (I) and metformin hydrochloride in which the instability of Compound (I) is inhibited or prevented.

Metformin hydrochloride is known to have poor inherent compressibility (United States Patent Number 6117451). This lack of compressibility, when combined with the large unit dosage requirements of metformin hydrochloride (500mg - 1000mg) results in significant formulation problems, especially in tablet formulation. The compressibility of metformin hydrochloride is usually improved by addition of a binding agent (or binder) which acts to bind the metformin hydrochloride particles into granules, the resultant granules having the flow and compressibility properties necessary for formulation.

In our hands we have found that polyvinyl pyrrolidone (or PVP) is particularly effective as a binder for use with metformin hydrochloride providing excellent flow and compressibility properties. However it is indicated that the use of PVP in formulations which also contain Compound (I) destabilise Compound (I). It is also indicated that the particular methodology used to prepare the PVP/Compound (I) formulations has an impact upon the stability of Compound (I).

In response to these findings we now provide Compound (I) formulations containing PVP in which Compound (I) shows good stability. In addition the compositions containing metformin show good compressibility characteristics.

5 The above mentioned compositions are considered to be particularly useful for the formulation of Compound (I) especially in combination with metformin hydrochloride. It is believed that all thiazolidinediones would be subject to similar decomposition due to the presence of metformin hydrochloride and/or PVP.

10 Accordingly, in a first aspect the invention provides a pharmaceutical composition, comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier in the pharmaceutical composition.

Suitably, the carrier for the thiazolidinedione, such as Compound (I), is different in composition to that of the carrier for metformin hydrochloride.

15 In one embodiment of the invention the thiazolidinedione and its carrier are substantially in admixture with the metformin hydrochloride and its carrier.

Suitably the thiazolidinedione and its carrier are substantially in homogenous admixture with the metformin hydrochloride and its carrier.

20 Suitably, the thiazolidinedione/carrier mixture is compacted with the metformin hydrochloride/carrier mixture in the composition, suitably to form a tablet. For example, the admixture of the thiazolidinedione/carrier mixture with the metformin hydrochloride/carrier mixture is compacted to form a tablet.

25 Preferably, the pre-formed thiazolidinedione/carrier mixture is admixed with the pre-formed metformin hydrochloride/carrier mixture on preparation of the composition of the invention. For example the thiazolidinedione/carrier mixture is admixed with the metformin hydrochloride/carrier mixture in a capsule form.

A suitable carrier for the thiazolidinedione comprises one or more components selected from: a binding agent, preferably other than PVP, a filler, a lubricants, a glidant, a disintegrant and a wetting agent.

30 Suitable carriers for the metformin hydrochloride comprises one or more components selected from: a binding agent, preferably PVP, a filler, a lubricants, a glidant, a disintegrant and a wetting agent.

35 The carrier for the metformin hydrochloride is as indicated preferably PVP but optionally at least one additional binder, for example hydroxypropylmethyl cellulose (or HPMC) is also used. In a particular preferred aspect when an additional binder or binders are used then the amount of PVP is the minimum required to provide the required compressability for metformin.

40 It is also envisaged that the thiazolidinedione and metformin hydrochloride can each be located in discrete zones with respect to each other, wherein each zone comprises the active agent and optionally a carrier.

Thus the invention also provides a pharmaceutical composition comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride, and, optionally, a

pharmaceutically acceptable carrier therefor, wherein the thiazolidinedione and metformin hydrochloride are located in discrete zones with respect to each other.

A layer provides a suitable zone, generally a compressed layer, of the active agent. Thus, the formulation may comprise layers, generally shaped layers of the active agents.

A suitable formulation is a tablet formulation. Thus one particular formulation is a multilayer tablet wherein the active agents are in separate layers. One particular formulation comprises a compressed form, for example a tablet, of one active agent formulated with a powdered form of the other active agent. The tablet and powder are generally encapsulated.

Preferably, the discrete zones are separated by a barrier layer, preferably an inert barrier layer. The barrier layer conveniently comprises a filler, such as lactose, and a lubricant, such as magnesium stearate.

The tablets containing active agents in discrete zones with respect to each other may be multilayer tablets. For example they may be bilayer tablets, where a layer of the granular form of one active agent is compressed, the granular form of the other active agent then added and compressed onto the layer of the first active agent. They may also be trilayer tablets prepared in an analogous manner.

As indicated, such compositions may conveniently be produced as tablets or capsules. Tablets may be produced by admixture of granular forms of the active agents followed by compression.

Granules of each active agent may be obtained by combination of the active agent with appropriate excipients, for example hydroxypropyl methyl cellulose, microcrystalline cellulose, sodium starch glycollate, lactose, and magnesium stearate, followed by granulation using conventional techniques.

Capsules may be produced by admixture of pelleted forms or granular forms of the active agents followed by encapsulation.

Pellets of each active agent may be obtained by combination of the active agent with appropriate excipients, for example microcrystalline cellulose and lactose, followed by pellet formation using conventional techniques. Granules are prepared as described herein. The production of tablets and capsules may be undertaken using techniques that are well known in the art.

Suitable dosages, preferably unit dosages, of thiazolidinediones such as Compound (I) and metformin hydrochloride include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

The dosages of each particular active agent in any given composition can as required vary within a range of doses known to be required in respect of accepted dosage regimens for that compound.

In one particular aspect, the composition comprises 2 to 12 mg of Compound (I).

Suitably the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4, 4 to 8, or 8 to 12 mg of Compound (I).

5 Particularly, the composition comprises 2 to 4mg of Compound (I).

Particularly, the composition comprises 4 to 8mg of Compound (I).

Particularly, the composition comprises 8 to 12 mg of Compound (I).

Preferably, the composition comprises 2 mg of Compound (I).

Preferably, the composition comprises 4 mg of Compound (I).

10 Preferably, the composition comprises 8 mg of Compound (I).

As indicated above the unit doses of metformin include those found in the reference texts mentioned herein and include the doses set out below.

A suitable dosage of metformin hydrochloride is between 100 to 3000mg, for example 250, 500mg, 850mg, or 1000mg.

15 Particular compositions of the invention comprise doses of Compound (I) in the range of from 2-12mg and metformin hydrochloride in the range of from 100 to 3000mg, for example 4mg of Compound (I) and 500mg of metformin hydrochloride. Other formulations comprise 2mg of Compound (I) and 500mg or 850mg of metformin hydrochloride or 4mg of Compound (I) and 850mg of metformin hydrochloride.

20 Other thiazolidinediones include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone), especially 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

The compounds mentioned herein, in particular thiazolidinediones such as Compound (I), may exist in one of several tautomeric forms, all of which are encompassed by the invention as individual tautomeric forms or as mixtures thereof. The compounds mentioned herein may contain one or more chiral carbon atoms and hence can exist in two or more stereoisomeric forms, all of which are encompassed by the invention either as individual isomers or as mixtures of isomers, including racemates.

30 It will be understood that thiazolidinediones such as Compound (I) and metformin are in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate to the relevant pharmaceutically active agent chosen. In certain instances herein the names used for the antidiabetic agent may relate to a particular pharmaceutical form of the relevant active agent. It will be understood that all pharmaceutically acceptable forms of the active agents *per se* are encompassed by this invention. Suitable pharmaceutically acceptable forms of thiazolidinediones such as 40 Compound (I) and metformin include known pharmaceutically acceptable forms. Such

derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above mentioned publications. For example, a particular form of metformin is metformin hydrochloride.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0 306 228 and WO 94/05659, especially pharmaceutically acceptable salted or solvated forms. A preferred pharmaceutically acceptable salt form of Compound (I) is a maleate. A preferred pharmaceutically acceptable solvated form of Compound (I) is a hydrate.

Metformin and metformin pharmaceutically acceptable forms are prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0 306 228 and WO 94/05659. The disclosures of EP 0 306 228 and WO 94/05659 are incorporated herein by reference.

It will be understood from the above that certain of the present compositions comprise a thiazolidinedione/carrier mixture substantially in admixture, suitably an homogenous admixture, with a metformin hydrochloride/carrier mixture.

The terms "admixture" and "mixture" are used interchangeably.

When used herein the term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance impaired fasting glucose and hyperinsulinaemia.

"Conditions associated with diabetes mellitus itself" include hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome, steroid induced insulin resistance and gestational diabetes.

"Complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term "pharmaceutically acceptable" embraces both human and veterinary use. For example, the term "pharmaceutically acceptable" embraces a veterinarily acceptable compound.

When used herein "carrier" means "pharmaceutically acceptable carrier".

5 For the avoidance of doubt, unless otherwise stated, when reference is made herein to scalar amounts, including mg amounts, of the active compound such as Compound (I), in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of the active compound *per se*. For example, 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt, which provides 2 mg of
10 Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using
15 standard methodology, for example those described in Tiescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390, and Frank P., "Monitoring the Diabetic Patient with Glycosolated Hemoglobin Measurements", Clinical Products 1988.

The compositions may be in the form of tablets, lozenges, suppositories, or capsules. Usually the compositions are adapted for oral administration. However, they
20 may be adapted for other modes of administration, for example sublingual or transdermal administration.

In a further aspect the invention also provides a process for preparing a pharmaceutical composition comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride, and a pharmaceutically acceptable carrier, in which the
25 thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier, which process comprises:
(i) admixing the thiazolidinedione and a pharmaceutically acceptable carrier;
(ii) admixing the metformin hydrochloride and a pharmaceutically acceptable carrier; and
(iii) formulating the thiazolidinedione/pharmaceutically acceptable carrier mixture with
30 the metformin hydrochloride /pharmaceutically acceptable carrier mixture.

Suitably, the carrier for the thiazolidinedione, such as Compound (I), has a different composition to that of the carrier for metformin hydrochloride.

In one aspect of the process of the invention, step (iii) of the process includes substantially admixing the thiazolidinedione/carrier mixture with the metformin
35 hydrochloride/ carrier mixture, suitably to provide an homogenous mixture of the thiazolidinedione/carrier mixture with the metformin hydrochloride/ carrier mixture.

The above mentioned process has a further advantage in that by pre-preparing the thiazolidinedione/carrier mixture and the metformin hydrochloride/ carrier mixture it allows greater accuracy of dosing in the final composition, especially as in the case of
40 Compound (I) compositions when there is a large differential between the thiazolidinedione and the metformin hydrochloride dosages.

In a further aspect of the process of the invention, for preparing a pharmaceutical composition comprising a thiazolidinedione/metformin hydrochloride composition

wherein the thiazolidinedione and the metformin hydrochloride are located in discrete zones with respect to each other, step (iii) of the process, comprises formulating the thiazolidinedione/carrier mixture and the metformin hydrochloride/carrier mixture into discrete zones with respect to each other.

5 A suitable zone is provided by forming a layer, generally via compression, of the active agent. Thus the formulation comprise forming layers, generally shaped layers of each active agent. Alternatively, step (iii) of the process comprises formulating a compressed form, for example a tablet, of one active agent with a powdered form of the other active agent, providing for example a tablet and powder which may then be
10 encapsulated according to normal practice for example in a capsule. For example a tableted form of Compound (I) is

Preferably, the discrete zones are separated by a barrier layer.

Tablets containing active agents in discrete zones with respect to each other are suitably formulate into multilayer tablets for example bilayer tablets. Such tablets are
15 conveniently formed by compressing a granular form of one active agent, the granular form of the other active agent is then added and then compressed onto the layer of the first active agent. Trilayer tablets are prepared in an analogous manner.

Granules of the active agent/carrier mixture are prepared using standard methodology.

20 Preferably, the compositions are in unit dosage form. Unit dosage presentation forms for oral administration may be tablets, lozenges, or capsules and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants and wetting agents.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose
25 calcium, carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, and tragacanth.

30 Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate,
35 magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, and xylitol.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium
40 chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, and zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, and talc.

Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrillin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, and sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate.

As required the compositions may be prepared by conventional methods of blending, tableting, or encapsulation. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

The invention also provides a composition according to the invention for use in a method for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

No adverse toxicological effects are expected for the compositions of the invention in the above mentioned dosage ranges.

The following examples illustrate the invention but do not limit it in any way.

Examples**a) Preparation of Metformin HCl Granules****Example 1: Metformin HCl Granules**

Metformin HCl is granulated with Polyvinyl pyrrolidone and the resultant granule dried and lubricated.

<u>Composition of Metformin HCl granule</u>	<u>mg</u>
Metformin HCl	500
Polyvinyl pyrrolidone	15 or 20
Magnesium stearate	5

Example 2: Metformin HCl high shear granulation

Metformin HCl is dry-blended with PVP and hydroxypropyl methylcellulose. The resultant mixture is wet granulated with purified water in a high shear mixer granulator. The wet granules are then screened, dried in a fluid bed drier and the dried granules are passed through a further screen.

<u>Composition of Metformin HCl granule</u>	<u>mg</u>
Metformin HCl	500
Polyvinyl pyrrolidone	5-20
HPMC	20-30

Example 3: Metformin HCl Spray granulation

Metformin HCl is dry blended with syloid then spray granulated with a solution of aqueous polyvinyl pyrrolidone. The resultant granule is screened.

<u>Composition of Metformin HCl granule</u>	<u>mg</u>
Metformin HCl	500
Polyvinyl pyrrolidone	10- 25
Syloid	2.5-25

b) Preparation of Metformin HCl pellets**Example 4: Metformin HCl pellets**

Metformin HCl, microcrystalline cellulose and lactose are blended then water added to wet. The wet mass is extruded and spheronised to give pellets. The pellets are then dried.

<u>Composition of Metformin HCl pellets</u>	<u>mg</u>
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Metformin HCl	500
Microcrystalline cellulose	75
Lactose	50

5

c) Preparation of granules of Compound (I) maleate salt

Example 5: Granules of compound (1)

10 Compound (I) hydroxypropyl methylcellulose, microcrystalline cellulose sodium starch glycollate and lactose are blended then wet granulated. The resultant granules are screened dried and further screened.

	<u>Composition)</u>	<u>mg</u>
15	Compound (I)	5.3
	Hydroxypropyl methyl cellulose	3.7
	Microcrystalline cellulose	30.0
	Sodium starch glycolate	7.5
	Lactose	102
20	Magnesium stearate	1.5

Example 6: Granules of compound (1)

	<u>Composition</u>	<u>mg</u>
25	Compound (I)	5.3
	(e.g. for 4mg of compound (1)	
	Hydroxypropyl methyl cellulose	3.7
	Microcrystalline cellulose	30.0
	Sodium starch glycolate	7.5
30	Lactose	102

Example 7: Granules of Compound (I) maleate salt (bilayer)

35 Compound (I) hydroxypropyl methylcellulose, microcrystalline cellulose sodium starch glycollate and lactose are blended then wet granulated. The resultant granules are screened dried and further screened, then blended with magnesium stearate.

40	<u>Composition of granules</u>	<u>mg</u>
	Compound (I)	5.3
	(eg equivalent to 4mg compound I)	
	Hydroxypropyl methyl cellulose	7.0
	Microcrystalline cellulose	48.0

Sodium starch glycolate	13.75
Lactose	198.20
Magnesium stearate	1.38-2.75

5 **Example 8: Granules of Compound (I) maleate salt (Press coat)**

Prepared as in example 7 above.

	<u>Composition of granules</u>	<u>mg</u>
10	Compound (I)	5.3
	Hydroxypropyl methyl cellulose	7.5
	Microcrystalline cellulose	60.0
	Sodium starch glycolate	15.0
	Lactose	238.9
15	Magnesium stearate	3.3

Example 9: Granular concentrate of Compound (I) maleate salt

20 Granules of each active agent, which include conventional binders, diluents, lubricants and glidants where appropriate, are compressed into a tablet.

	<u>Concentrate Granules of Compound (I)</u>	<u>mg</u>
	Compound (I)	5.3
	Hydroxypropyl methyl cellulose	2.0
25	Microcrystalline cellulose	8.0
	Sodium starch glycolate	2.0
	Lactose	22.7

Example 10: Granular concentrate of Compound (I) maleate salt

30 Approximately two thirds of the lactose monohydrate is passed through a suitable screen and blended with the milled maleate salt of Compound (I).
Sodium starch glycollate, hydroxypropyl methylcellulose, microcrystalline cellulose and the remaining lactose are passed through a suitable screen and added
35 to the mixture. Blending is then continued. The resulting mixture is then wet granulated with purified water. The wet granules are then screened, dried on a fluid bed drier and the dried granules are passed through a further screen and finally homogenised.

40 **Composition of granular concentrate**

Ingredient	Quantity (%)
Milled Compound (I) as	13.25 (pure

maleate salt	maleate salt)
Sodium Starch Glycollate	5.00
Hydroxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

Example 11: Compression blend of Compound (I) maleate salt

The granules from Example 10 are placed into a tumble blender. Approximately two thirds of the lactose is screened and added to the blender. The microcrystalline cellulose, sodium starch glycollate, magnesium stearate and remaining lactose are screened and added to the blender and the mixture blended together.

Composition of compression blend

Tablet Strength	Quantity (mg per dosage form)		
	1.0mg	2.0mg	4.0mg
Active Ingredient:			
Compound (I) maleate Concentrate granules from example 10	10.00	20.00	40.00
Other Ingredients:			
Sodium Starch Glycollate	6.96	6.46	5.46
Microcrystalline Cellulose	27.85	25.85	21.85
Lactose monohydrate	104.44	96.94	81.94
Magnesium Stearate	0.75	0.75	0.75

Example 12: Tablets of Compound (I) maleate salt

<u>Composition</u>	<u>mg</u>
Compound I	5.3
Hydroxypropyl methyl cellulose	2.5- 5.0
Microcrystalline cellulose	20.0

Sodium starch glycolate	5.0
Lactose	66.2
Magnesium stearate	1.0

5 Example 13: Tablets of compound 1

The compression blend produced as in example 11 is compressed on a rotary tablet press to a target weight of 150mg for the 1, 2 and 4mg tablets and to a target weight of 300mg for the 8mg tablets.

10 The tablet cores are then transferred to a tablet coating machine, pre-warmed with warm air (approximately 65°C) and film coated until the tablet weight has increased by 2.0% to 3.5%.

15 Composition of tablets of Compound (I) maleate salt

Tablet Strength	Quantity (mg per Tablet)			
	1.0mg	2.0m	4.0mg	8.0mg
	g			
Active Ingredient:				
Compound (I) maleate Concentrate granules from Example 10	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose	27.85	25.85	21.85	43.70
Lactose monohydrate	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Aqueous film coating material	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

20 d) Preparation of pellets of Compound (I) maleate salt

Compound (I), microcrystalline cellulose and lactose are blended then water added. The wet mass is extruded and spheronised to give pellets. The pellets are dried.

25 Example 14: Pellets of Compound (I)

	<u>Composition of pellets</u>	<u>mg</u>
	Compound (I)	5.3
	Microcrystalline cellulose	25.0
5	Lactose	19.7

e) **Preparation of Compound (I) maleate salt /Metformin HCl tablets**

(i) Direct compression

10 Metformin HCl granules and either Compound (I) maleate salt granules or
Compound (I) maleate salt compression blends are mixed in the appropriate ratio
to give the desired tablet strength of combination tablet with microcrystalline
cellulose and magnesium stearate. The final compression blend is compressed into
15 tablets and aqueous film coated.

Example 15: Compound (I) maleate salt/Metformin HCl tablets

	<u>Tablet Formula</u>	<u>mg/tablet</u>
20	Granules of Compound (I) (equivalent to 4mg pfb) (see example 5)	150
	Granules of metformin HCl, see example 1 (equivalent to 500mg metformin HCl)	520 or 525

25 **Example 16: Compound (I) maleate salt/Metformin HCl tablets**

	<u>Tablet Formula</u>	<u>mg/tablet</u>
	Granules of Compound (I) (equivalent to 4mg pfb) (see example 9)	40
30	Granules of metformin HCl (equivalent to 500mg metformin HCl) (see example 1)	525

35 **Example 17: Compound (I) maleate salt/Metformin HCl tablets**

	<u>Tablet formula</u>	<u>Amount %</u>
40	Metformin HCl granules (examples 1,2 or 3) (equivalent to 500mg Metformin HCl)	As required
	Compound (I) maleate salt granules (examples 5,6,9,10,11) (equivalent to 1, 2 or 4mg Compound (I))	As required
	Microcrystalline cellulose	4-7%

Magnesium stearate 0.5%

Example 18: Compound (I) maleate salt/Metformin HCl tablets

5	<u>Tablet formula</u>	<u>Amount %</u>
	Metformin HCl granules (examples 1,2 or 3) (equivalent to 500mg Metformin HCl)	As required
	Compound (I) maleate salt granules (examples 5,6,9,10,11) (equivalent to 1, 2 or 4mg Compound (I))	As required
10	Hydroxypropyl methylcellulose	4-7%
	Magnesium stearate	0.5%

(ii) Mixed pellets or granules in a capsule

15 Pellets or granules of Compound (I) and metformin HCl are combined, lubricated and filled into a hard gelatin capsule.

Example 19: Mixture of pellets

20	<u>Composition</u>	<u>mg/capsule</u>
	Pellets of Compound (I) (example 14, e.g. equiv. to 4mg)	50
	Pellets of metformin HCl (example 4) (equivalent to 500mg metformin HCl)	625

25

Example 20: Mixture of pellets

30	<u>Composition</u>	<u>mg/capsule</u>
	Pellets of Compound (I) (example 14, e.g. equiv. to 4mg)	50
	Pellets of metformin HCl (example 4) (equivalent to 500mg metformin HCl)	625
	Magnesium stearate	3.4

35

Example 21: Mixture of granules

40	<u>Composition</u>	<u>Amount</u>
	Metformin HCl granules (examples 1,2,3) (equivalent to 500mg Metformin HCl)	As required
	Compound (I) maleate salt granules (examples 5,6,9,10,11)	

(equivalent to 1, 2 or 4mg Compound (I))	As required
Magnesium stearate	0.5%

(iii) Encapsulation of tablet of Compound (I) maleate salt

A tablet of Compound (I) maleate salt of the desired strength, example 7, is filled into an appropriate sized capsule shell and overfilled with metformin hydrochloride (blended with magnesium stearate) or a Metformin HCl granule, see example 1 or 2, equivalent to 500mg.

Example 22: Compound (I) maleate salt/Metformin HCl capsule

<u>Composition</u>	<u>mg/capsule</u>
Tablet of Compound (I) maleate salt (example 12)	150
(equivalent 4mg Compound (I))	
Metformin hydrochloride	500mg

Example 23: Compound (I) maleate salt/Metformin HCl capsule

<u>Composition</u>	<u>mg/capsule</u>
Tablet of Compound (I) maleate salt (example 12, 13)	1 tablet
(equivalent to 1, 2 or 4mg Compound (I))	
Metformin hydrochloride	500mg
Magnesium stearate	2.5mg

Example 24: Compound (I) maleate salt/Metformin HCl capsule

<u>Composition</u>	<u>Amount</u>
Tablet of Compound (I) maleate salt (example 12,13)	1 tablet
(equivalent to 1, 2 or 4mg Compound (I))	
Metformin HCl granules (examples 1,2,3)	As required
(equivalent to 500mg Metformin HCl)	

(iv) Bi and tri layer tablets

Granules of metformin hydrochloride and Compound (I) are compressed as discrete layers to form a bilayer tablet. Granules of metformin hydrochloride and Compound (I) are compressed as discrete layers that are separated by a barrier layer to form a trilayer tablet.

Example 25: A bilayer tablet

	<u>Bilayer tablet composition</u>	<u>Amount (mg)</u>
	Metformin HCl granules (examples 1,2 or 3) (equivalent to 500mg Metformin HCl)	520-540
5	Compound (I) maleate salt granules (examples 7 or 5,6,9,10,11) (equivalent to 1, 2 or 4mg Compound (I))	275

Example 26: A trilayer tablet

10	<u>Barrier layer (non active)</u>	<u>mg</u>
	Lactose	198
	magnesium stearate	1-2
	<u>Trilayer tablet formulation</u>	<u>Amount (mg)</u>
15	Metformin HCl granules (examples 1, 2 or 3) (equivalent to 500mg Metformin HCl)	520-540
	Barrier layer	200
	Compound (I) maleate salt granules (examples 8 or 5,6,9,10,11) (equivalent to 1, 2 or 4mg Compound (I))	275

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(v) Press coated tablets

Compound (I) is applied by a press coating procedure around a pre formed Metformin HCl tablet, or, Metformin hydrochloride is applied by a press coating procedure around a pre formed tablet of Compound (I)

25

Example 27: Press coated tablet; Compound (I) maleate salt as press coat

A granule of compound I equivalent to 1mg, 2mg or 4mg of Compound (I) maleate salt is press coated onto a pre-formed metformin hydrochloride tablet

30

Metformin HCl tablet 500mg

(formed by blending granules of metformin Hydrochloride prepared as in examples 1, 2 or 3 with magnesium stearate, then compressing into tablets)

35

	<u>Formula</u>	<u>mg/tablet</u>
	Metformin HCl tablet (equivalent to 500mg metformin hydrochloride)	520-540
40	Press coat of Compound (I) maleate salt, example 8 (equivalent to 4mg Compound (I))	330

Example 28: Press coated tablet; Metformin hydrochloride as press coat

A granule of metformin hydrochloride, equivalent to 500mg is press coated onto a pre formed tablet of Compound (I) maleate salt, see example 13

	<u>Formula</u>	<u>mg/tablet</u>
5	Tablet of Compound (I) maleate salt (equivalent to 1,2 or 4mg Compound 1)	154.5
	Metformin hydrochloride granule, example 1, 2 (equivalent to 500mg metformin hydrochloride)	535
	Magnesium stearate	2.7

Claims.

1. A pharmaceutical composition, comprising a thiazolidinedione, such as
5 Compound (I), metformin hydrochloride and a pharmaceutically acceptable carrier,
wherein the thiazolidinedione and metformin hydrochloride are each dispersed within its
own pharmaceutically acceptable carrier in the pharmaceutical composition.
2. A composition according to claim 1, wherein the carrier for the thiazolidinedione,
10 is different in composition to that of the carrier for metformin hydrochloride.
3. A composition according to claim 1 or claim 2, wherein the thiazolidinedione and
its carrier are substantially in admixture with the metformin hydrochloride and its carrier.
- 15 4. A composition according to any one of claims 1 to 3, wherein the
thiazolidinedione and its carrier are substantially in homogenous admixture with the
metformin hydrochloride and its carrier.
5. A composition according to any one of claims 1 to 4, wherein the
20 thiazolidinedione/carrier mixture is compacted with the metformin hydrochloride/carrier
mixture in the composition.
6. A composition according to any one of claims 1 to 5, wherein the composition is
in the form of a tablet.
- 25 7. A composition according to any one of claims 1 to 6, wherein the carrier for the
thiazolidinedione comprises one or more components selected from: a binding agent other
than PVP, a filler, a lubricants, a glidant, a disintegrant and a wetting agent.
- 30 8. A composition according to any one of claims 1 to 7, wherein the carrier for the
metformin hydrochloride comprises one or more components selected from: a binding
agent being PVP, a filler, a lubricants, a glidant, a disintegrant and a wetting agent.
9. A composition according to claim 8, wherein the carrier for the metformin
35 hydrochloride comprises at least one additional binder.
10. A composition according to claim 9, wherein the amount of PVP is the minimum
required to provide the required compressibility for metformin.
- 40 11. A composition according to claim 1, wherein the thiazolidinedione and metformin
hydrochloride are located in discrete zones with respect to each other and wherein each
zone comprises the active agent and optionally a carrier.

- 5 12. A composition according to claim 11, each zone is a compressed layer.
13. A composition according to claim 11 or 12, in the form of a multilayer tablet wherein the active agents are in separate layers.
- 10 14. A composition according to any one of claims 11 to 13, wherein the discrete zones are separated by a barrier layer.
15. A composition according to claim 13, wherein the barrier layer comprises a filler, and a lubricant.
- 15 16. A composition according to claim 11, wherein one zone is a compressed layer and the other is in a powder form.
17. A composition according to claim 16, wherein the compressed layer is a tablet and
20 the tablet and powder are encapsulated in a capsule form.
18. A composition according to any one of claims 1 to 17, wherein thiazolidinedione is selected from: Compound (I) or include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or
25 troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone), especially 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).
- 30 19. A composition according to any one of claims 1 to 19, wherein the composition comprises 2 to 12 mg of Compound (I).
20. A composition according to any one of claims 1 to 19, wherein the
35 composition comprises 100 to 3000mg of metformin hydrochloride.
21. A process for preparing a pharmaceutical composition according to claim 1, comprising a thiazolidinedione and metformin hydrochloride which process comprises:
- 40 (a) for a composition wherein the thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier,
(i) admixing the thiazolidinedione and a pharmaceutically acceptable carrier;

(ii) admixing the metformin hydrochloride and a pharmaceutically acceptable carrier; and

(iii) formulating the thiazolidinedione/pharmaceutically acceptable carrier mixture with the metformin hydrochloride /pharmaceutically acceptable carrier mixture or

5

(b) for a composition wherein the thiazolidinedione and the metformin hydrochloride are located in discrete zones with respect to each other, step (iii) of the above process, comprises formulating the thiazolidinedione/carrier mixture and the metformin hydrochloride/carrier mixture into discrete zones with respect to each other.

10

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(57) Abstract: A pharmaceutical composition, comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier in the pharmaceutical composition and the use of such a composition in medicine.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 03477 A (SMITHKLINE BEECHAM) 28 January 1999 (1999-01-28) claims 1,3-5 page 6, line 8-19 page 7, line 9-12	1,6, 18-20
A	WO 98 57634 A (SMITHKLINE BEECHAM) 23 December 1998 (1998-12-23) claims 1-5,13 page 5, line 30 -page 6, line 3 page 6, line 19-26	1,6, 18-20

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903477 A	28-01-1999	AU 8448898 A	10-02-1999
		BG 104135 A	31-10-2000
		BR 9810445 A	05-09-2000
		CN 1264303 T	23-08-2000
		EP 1001783 A	24-05-2000
		NO 20000228 A	17-01-2000
		PL 338126 A	25-09-2000
		SK 592000 A	12-09-2000
		TR 200000134 T	21-09-2000
WO 9857634 A	23-12-1998	AU 8539398 A	04-01-1999
		BG 104060 A	31-10-2000
		BR 9810172 A	08-08-2000
		CN 1260716 T	19-07-2000
		EP 0996444 A	03-05-2000
		NO 996266 A	17-12-1999
		PL 337362 A	14-08-2000
		TR 9903057 T	21-04-2000
		HU 0002668 A	28-12-2000